REMARKS

Claims 1, 3-10, 12, 35-37, and 39-46, 49, and 51 are pending in the present application, wherein claims 44-46 and 51 have been withdrawn from consideration.

The Presently Claimed Invention

The present invention relates to a pharmaceutical tablet that (i) contains a crystalline amlodipine free base and (ii) exhibits a specified low punch residue. Neither feature is taught in the applied prior art. To the contrary, the prior art teaches that amlodipine free base has inferior tabletting characteristics in comparison to certain salts of amlodipine such as the besylate salt of amlodipine. (See Davison col. 3, line 30 *et seq.*) But whereas the Davison patent teaches amlodipine free base to have a tablet residue of 2.02 and amlodipine besylate a residue of 1.17, the present invention is limited to tablets that have an average punch residue of 0.7 $\mu g \cdot cm^{-2}$ per tablet or less. That an amlodipine free base-containing tablet can exhibit such low punch residue, both in the same formulation as tested in Davison (See the Vanderheijden Declaration) and in other formulations (see Example 9 of the instant specification) is unexpected. The low punch residue is believed to be due to the use of crystalline amlodipine free base, especially crystalline form I, as opposed to amorphous or partly amorphous-partly crystalline amlodipine free base. It should be noted that the use of crystalline amlodipine free base in a tablet is novel. Indeed, the USPTO has determined crystalline amlodipine free base *per se* to be patentable. (See the later filed, earlier issued patent to Bentham *et al.*) The combination of the crystalline and punch residue features clearly make independent claims 1 and 13 novel and patentable.

Rejection over Young under § 103

Claims 1, 3-10, 12, 35-37, 39-43, and 49 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. patent 6,057,344 (Young). This rejection is respectfully traversed.

Young fails to teach or suggest the formation of crystalline amlodipine free base. Example 8, now relied upon exclusively by the Examiner, teaches a recipe for making tablets wherein the amount of the active ingredient is recited. Specifically Example 8 indicates "Active ingredient, (-)amlodipine." This disclosure does not state that the amlodipine is crystalline nor does it teach that the free base is used.

Young frequently uses the word "amlodipine" to mean an amlodipine salt. For example, column 2 lines 1-6 refers to amlodipine being "available commercially only as the 1:1 racemic mixture" and then clarifies that the commercially available amlodipine is a besylate salt. Similarly, column 2 lines 63 et seq. and column 8 lines 3-11 are two further illustrations where Young uses the word "amlodipine" to clearly refer to the besylate salt of amlodipine. Furthermore, Young teaches that the (-) amlodipine is "most conveniently isolated as a salt" in column 10 lines 15-18. Thus, Young uses "amlodipine" as short hand for both the free base and the salts thereof. Therefore, the "(-)amlodipine," mentioned in Young Example 8 would have been understood to mean amlodipine and its salts and is not an example of an amlodipine free base tablet *per se*.

And if the worker of ordinary skill in the art understood Young to be suggesting the use of the free base of amlodipine, why would the worker believe the amlodipine free base was crystalline? Young does not teach crystalline amlodipine free base or its

formation. Instead, Young teaches isolating amlodipine as a salt, e.g. precipitating a salt form of amlodipine from the amlodipine reaction mixture.

Finally, given the disclosures in the prior art that amlodipine free base is inferior in punch residue, the worker of ordinary skill in the art would have no basis for expecting to form a tablet composition of amlodipine free base with superior punch residue as recited by the present claims. That is, forming an amlodipine free base tablet with the presently claimed low punch residue is *per se* unexpected. Nothing in Young contradicts the teachings in Davis regarding amlodipine free base or otherwise leads the average artisan to either (i) expect a great improvement in punch residue through the use of crystalline material or (ii) believe that a crystalline amlodipine free base is even possible to be formed.

The Examiner argues that the amlodipine free base used in Young Example 8 has not been shown to be purely amorphous. But applicants are under no such burden. Rather, applicants simply point out that amlodipine free base in crystalline form is not taught in Young. It is the Examiner's burden to show where the prior art suggests the use of applicants' claimed crystalline material.

Next the Examiner ducks the crystallinity requirement and attacks the low punch residue feature because the data is allegedly based on only two formulations. But this attack is irrelevant to the obviousness determination. Compositions that fail to exhibit the claimed average punch residue are simply outside the scope of the present claims. The fact that specific excipients are not recited does not render the claimed functional requirement moot. The question for the Examiner is not whether applicants have shown that all excipients work well or not, but rather, whether the prior art suggests that an

amlodipine free base tablet composition could have good processability, e.g., a punch residue less than that achieved by the besylate salt of amlodipine? The answer is clearly "no;" there is no suggestion of forming such a composition with amlodipine free base. Thus the Examiner is without a valid reason to refuse to allow the present claims.

In view of the failure of Young to teach or suggest an amlodipine free base tablet composition having (1) crystalline amlodipine free base, especially form I, and (2) a low punch residue, and in view of the teaching in the prior art that amlodipine free base tablets have inferior punch residue, the presently claimed subject matter could not have been obvious to a worker of ordinary skill in the art. Accordingly, the presently claimed subject matter is unobvious over Young and reconsideration and withdrawal of this rejection are respectfully requested.

Rejection over Lazar and Davison

Claims 1, 3-10, 12, 35-37, 39-43, and 49 have been rejected under 35 U.S.C. § 103(a) over U.S. patent 5,155,120 (Lazar) in combination with U.S. patent 4,879,303 (Davison). This rejection is respectfully traversed.

Neither Lazar nor Davison teach a pharmaceutical tablet containing crystalline amlodipine free base and having an average punch residue of 0.7 $\mu g\ cm^{-2}$ per tablet or less as claimed in claims 1 and 43 of the present application. Nonetheless the Examiner erroneously argues that Lazar suggests using crystalline amlodipine free base and that "applicant has not shown any unexpected results obtained by using the crystalline forms." The Examiner's argument ignores the fact that claims 1 and 43 require the tablet composition to exhibit an unexpected result; namely an average punch residue of 0.7 $\mu g\ cm^{-2}$ per tablet or less. Why is this punch residue unexpected? Because Davis teaches a

punch residue for amlodipine free base tablets of 2.02 μg cm^{-2} per tablet. The fact that the inventive amlodipine free base tablets exhibit a punch residue less than the punch residue of the besylate salt of amlodipine is truly surprising given the teachings in Davis.

The Examiner's assertions that perhaps it would have been possible to make such a low punch residue tablet with an amorphous free base is speculative and, more importantly, misses the point. The prior art was not silent on the usefulness of amlodipine free base: it taught the free base of amlodipine to be inferior in processability to the besylate salt of amlodipine. The present claims require a surprisingly low punch residue. Nothing in the Examiner's position explains why the average artisan would have found it obvious that the prior art teachings could be turned upside down.

Similarly, the Examiner notes as "interesting" that the present specification generally teaches any form of amlodipine can be used. The Examiner see this as a contradiction. The Examiner is mistaken. The claims have been amended to define a preferred embodiment, one that excludes amorphous forms of amlodipine free base and that requires the tablet composition to exhibit a surprisingly low punch residue. There is no contradiction.

Accordingly, the presently claimed subject matter could not have been obvious to the worker of ordinary skill in the art at the time that the present invention was made. Reconsideration and withdrawal of this rejection are requested.

Rejection over Lazar and Young

Claims 1, 3-10, 12, 35-37, 39-43, and 49 have been rejected under 35 U.S.C. § 103(a) over Lazar in combination with Young. This rejection is respectfully traversed.

The Examiner alleges that Lazar lacks only a teaching of microcrystalline cellulose and other excipients to make the claimed invention as recited in several of the dependent claims. Young is applied as providing these deficiencies. This position is in error.

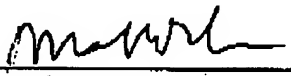
Contrary to the Examiner's position, Lazar fails to teach or suggest crystalline amlodipine free base. Indeed, although the Example in Lazar recites "amlodipine," this is actually a reference to the besylate salt of amlodipine. (See col. 3, lines 29-31) In any event, Lazar relates to a new use of amlodipine and not to the disclosure of a crystalline form of amlodipine free base, the latter not being taught or suggested. Additionally, Lazar fails to teach or suggest an amlodipine free base tablet having a low punch residue as claimed in claims 1 and 43. Young does not overcome these deficiencies for the reasons set forth above. Accordingly, the instant rejection fails to establish a *prima facie* case of obviousness. Therefore, reconsideration and withdrawal of this rejection are requested.

Conclusion

In view of the above amendments and remarks, all claims pending in the present application define novel, patentable subject matter. Reconsideration of the rejections and allowance of the application are respectfully requested.

Should the Examiner have any questions regarding this application, he is encouraged to contact Mark R. Buscher (Reg. No. 35,006) at telephone No. 703 753 5256.

Respectfully submitted,



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